REMARKS

Claims 1-29, 38-76, 82-92 and 108-119 are pending in the present application. Claims 1, 18, 47-52, 55, 65, 108, 115, 116, and 119 have been amended. Claims 30-37, 41, 46, 77-81, 93-107 and 120 have been cancelled without prejudice or disclaimer to the subject matter therein.

Applicants respectfully submit that as amended each of the presently pending claims presently include a granulate and a hydroxypropylmethyl cellulose external to the granulate.

In this regard, claim 1 has been amended to recite "A sustained release solid dosage form comprising: a) a granulate comprising a uniform admixture of: (i) an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide and a compound having the structure: [formula omitted] or [formula omitted] wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; and (ii) a binder; and b) a hydroxypropylmethyl cellulose external to the granulate. Support for amended claim 1 can be found, for example, at paragraphs 376, 377 and 423-425, as well as Tables 1 and 2 of the presently published application, as well as throughout the specification and claims as originally filed.

Additionally, claim 18 has been amended to recite "A sustained release solid dosage form comprising: a) a granulate comprising a uniform admixture of: (i) N-(2-Propylpentanoyl)glycinamide; and (ii) a binder; b) a hydroxypropylmethyl

cellulose external to the granulate; and c) a different hydroxypropylmethyl cellulose. Support for amended claim 18 can be found, for example, at paragraphs 376, 377 and 423-425, as well as Tables 1 and 2 of the presently published application, as well as throughout the specification and claims as originally filed.

Further, claim 38 has been amended to recite "A tablet, comprising: a) a granulate comprising a uniform admixture of: (i) an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide and a compound having the structure: [formula omitted] or [formula omitted] wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; and (ii) a hydroxypropylmethyl cellulose; and b) an additional hydroxypropylmethyl cellulose external to the granulate. In view of the amendment to claim 38, the term "composition" has been deleted without prejudice or disclaimer and replaced with the term "tablet" in claims 39 and 40. Additinally, further to the amendment to claim 38, claims 47-52 have been amended to recite "another hydroxylmethylpropyl cellulose" and "another hydroxylmethylpropyl cellulose," where necessary. Support for amended claims 38, 39, 40 and 47-52 can be found, for example, at paragraphs 376, 377 and 423-425, as well as Tables 1 and 2 of the presently published application, as well as throughout the specification and claims as originally filed.

In addition, claim 55 has been amended to recite "A sustained release tablet, comprising: a granulate comprising a compound having the structure: [formula omitted] or [formula omitted] wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; and a hydroxypropylmethyl cellulose external to the granulate. Support for amended claim 55 can be found, for example, at paragraphs 376, 377 and 423-425, as well as Tables 1 and 2 of the presently published application, as well as throughout the specification and claims as originally filed.

Moreover, claim 65 has been amended to recite "A process for preparing the solid dosage form of claim 1, comprising: a) forming a granulate by admixing predetermined amounts of (i) an active ingredient selected from the group consisting of valproic sodium acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, valpromide and a compound having the structure: [formula omitted] or [formula omitted] wherein R_1, R_2, and R_3 are independently the same or different and are hydrogen, a C_1-C_6 alkyl group, an aralkyl group, or an aryl group, and n is an integer which is greater than or equal to 0 and less than or equal to 3; and (ii) a binder; b) admixing the uniform mixture of step a) with a predetermined amount of a hydroxypropylmethyl cellulose; and c) compressing the mixture of step b) to form the tablet, wherein the hydroxypropylmethyl cellulose is external to the granulate." Support for amended claim 65 can be found, for example, at paragraphs 376, 377 and 423-425, as well

as Tables 1 and 2 of the presently published application, as well as throughout the specification and claims as originally filed.

Additionally, claim 108 has been amended to recite "A controlled release oral unit dose composition, comprising: a granulate comprising N-(2-propylpentanoyl)glycinamide and at least one pharmaceutically acceptable carrier; and a hydroxypropylmethyl cellulose external to the granulate, wherein the composition when orally ingested by a human subject, induces a peak blood plasma level of N-(2-propylpentanoyl)glycinamide between 4 and 24 hours after ingestion of a single oral unit dose. Support for amended claim 108 can be found, for example, at paragraphs 376, 377 and 423-425, as well as Tables 1 and 2 of the presently published application, as well as throughout the specification and claims as originally filed.

Further, claim 115 has been amended to recite "A controlled release oral unit dose composition, comprising: a granulate comprising N-(2-propylpentanoyl)glycinamide and a pharmaceutically acceptable carrier; and a hydroxypropylmethyl cellulose external to the granulate, wherein the composition when orally ingested by a human subject, induces a peak blood plasma level of N-(2-propylpentanoyl)glycinamide is from 0.5 μg/ml to 1.7 μg/ml per a 1000 mg dose of N-(2-propylpentanoyl)glycinamide in the composition. Support for amended claim 115 can be found, for example, at paragraphs 376, 377 and 423-425, as well as Tables 1 and 2 of the presently published application, as well as throughout the specification and claims as originally filed.

Furthermore, claim 116 has been amended to recite "A method of inducing in a human subject a peak blood plasma level of N-(2-propylpentanoyl)glycinamide between 4 and 24 hours after administration of N-(2-propylpentanoyl)glycinamide, comprising: administering to the human subject a controlled release oral unit dose composition, the controlled release oral unit does composition, comprising a granulate comprising N-(2-propylpentanoyl)glycinamide and at least one pharmaceutically acceptable carrier; and a hydroxypropylmethyl cellulose external to the granulate, wherein the controlled release oral unit does composition induces a peak blood plasma level of N-(2-propylpentanoyl)glycinamide between 4 and 24 hours after administration of a single oral unit dose. Support for amended claim 116 can be found, for example, at paragraphs 376, 377 and 423-425, as well as Tables 1 and 2 of the presently published application, as well as throughout the specification and claims as originally filed.

Also, claim 119 has been amended to correct a typographical error. Specifcally, the term "glycine" has been replaced with the term "glycinamide." Support for amended claim 119 can be found throughout the specification and claims as originally filed.

No new matter has been added.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. At page 3 of the Official Action, claims 1-29, 38-76, 82-92 and 108-119 have been provisionally rejected under on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-55 of co-pending application no. 10/772,911 in view of US Patent No. 4,704,285 (the '285 patent).

The Examiner asserts the presently pending claims and the claims of co-pending application no. 10/772,911 are each "directed to compressible tablets comprising valproic acids or its salts as an active ingredient, excipients such as HPMC, magnesium state, fillers, lubricants, etc." *See* Official Action at page 3. However, the Examiner further indicates that the present claims differ from the co-pending claims because the present claims recite HPMC in addition to the binder, whereas the co-pending claims recite hydroxypropyl cellulose and a disintegrant. Additionally, the Examiner indicates that the present claims differ from the co-pending claims because, in contast to the co-pending claims, the present claims include the elements related to viscosity and the the methoxy or hydroxypropyl content of HPMC. Additionally, the Examiner indicates that while the presently pending claims are directed to sustained release dosage forms, the co-pending claims are directed to immediate release dosage forms. However, in view of the several differences enumerated by the Examiner, the Examiner asserts that it would have been obvious to include HPMC such as described in the '285 patent in the compressible composition of the present claims because "all of the references are directed to compressible tablets and '285 teach that the claimed HPMC are routinely employed in compressible tablet preparation for improving flow properties of thee tablet."

Responsive to the double patenting rejection, Applicants respectfully request that this rejection be held in abeyance until an indication of allowable claims in this, or the co-pending application, is given.

II. At page 5 of the Official Action, claims 1-4, 7-11, 14-20, 29, 28-46, 53-72, 76, 82-89 and 108-119 have been rejected under 35 USC 103(a) as being unpatentable over either US Patent Application Publication No. 2001/0005512 (Anderson) in view of Remington's Pharmaceutical Sciences (1990) or US Patent No. 6,419,953 (Qui et al.) in view of Remington's Pharmaceutical Sciences (1990).

The Examiner asserts that it would have been obvious to a person of skill in the art to use the a single or more than one binder of Remington's in the compression tabletting composition of Anderson or Qiu because Remington's teach that binders impart cohesiveness to tablet formulations, which ensures that the tablet remains intact after compression, as well as improving the free flowing qualities by the formulation of granules of desired hardness and size.

In view of the following, Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U. S. ____ (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent

reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

It is submitted that a *prima facie* case of obviousness has not been established because whether taken alone, or in combination, neither of Anderson, Qui et al. and Remington's teach or suggest every element of the presently pending claims as required by *In re Wilson*.

As amended, Applicants submit that each of the presently pending claims presently include ***a granulate and a hydroxypropylmethyl cellulose external to the granulate***. According to the present subject matter, the granulate may comprise an active ingredient and a binder. Although, according to the present subject matter, the binder may be a hydroxypropylmethyl cellulose, Applicants note that the present subject matter also includes additional hydroxypropylmethyl cellulose external to, i.e., separate from, the granulate. Applicants respectfully

submit that as a result of the presently recited granulate and HPMC external to the granulate: the desired dissolution profile of a tablet according to the present subject matter may vary without remaking the granule composition; the granulate can be manufactured in bulk and than many batches of a tablet may be prepared, each having a different dissolution profile depending on the amount of HPMC added to the mixture; and no specific granulete size is required for the resulting tablets and consequently, the process of manufacture is significantly easier to implement than a process in which the HPMC is part of the granule composition.

In contrast to the presently claimed subject matter, Anderson is directed to an oral polymeric controlled release formulation suitable for the once-a-day administration of valproate compounds, such as divalproex sodium. *See* Anderson at the abstract. However unlike the presently claimed subject matter, Anderson does not teach or suggest a granulate and a hydroxypropylmethyl cellulose external to the granulate. In this regard, Anderson merely describes the pressing of HPMC into a tablet formulation with an active agent (divalproex). *See* Anderson at page 9, paragraphs [0108] to [0110]). Therefore, as Anderson does not teach or suggest a granulate and a hydroxypropylmethyl cellulose external to the granulate, Anderson does not render the presently claimed subject matter obvious.

Also in contradistinction to the presently claimed subject matter, Qui et al. is directed a hydrophilic matrix tablet suitable for the once-a-day administration of valproate compounds. The tablet of Qui et al. comprises from about 50 weight

percent to about 55 weight percent of an active ingredient selected from the group consisting of valproic acid, a pharmaceutically acceptable salt or ester of valproic acid, divalproex sodium, and valpromide; from about 20 weight percent to about 40 weight percent hydroxypropyl methylcellulose; from about 5 weight percent to about 15 weight percent lactose, from about 4 weight percent to about 6 weight percent microcrystalline cellulose, and from about 1 weight percent to about 5 weight percent of silicon dioxide. However unlike the presently claimed subject matter, Qui et al. do not teach or suggest a granulate and a hydroxypropylmethyl cellulose external to the granulate. In this regard, Qui et al. teach that microcrystalline cellulose is added externally to granules; however, the microcrystalline cellulose is not a part of the granule. *See* Qui et al. at col. 7, lines 8-11. Therefore, as Qui et al. do not teach or suggest a granulate and a hydroxypropylmethyl cellulose external to the granulate, Qui et al. do not render the present claimed subject matter obvious.

Remington's does not remedy the deficiencies of either Anderson or Qui et al. Remington's merely describes ingredients used in compressed tablets. However, like Anderson and Qui et al., Remington's also do not teach or suggest a granulate and a hydroxypropylmethyl cellulose external to the granulate, as presently claimed. Therefore, whether taken alone or in combination, neither Anderson and Remington's nor Qui et al. and Remington's teach or suggest every element of the presently pending claims.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, neither Anderson and Remington's nor Qui et al. and Remington's render claims the presently claimed subject matter obvious within the meaning of 35 USC § 103 (a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

III. At page 5 of the Official Action, claims 5-6, 12-13, 21-28, 47-52, 73-75 and 90 have been rejected under 35 USC 103(a) as being unpatentable over either Anderson in view of Remington's Pharmaceutical Sciences (1990) or Qui et al) in view of Remington's Pharmaceutical Sciences (1990) as applied to claims 92 1-4, 7-11, 14-20, 29, 28-46, 53-72, 76, 82-89 and 108-119, and in further view of US Patent No. 4,704,285(Alderman).

The Examiner asserts that it would have been obvious to a person of skill in the art to include HPMC as in the compressible composition of Anderson or Qui et al. because all of the references allegedly are directed to compressible tablets and Alderman allegedly teaches that HPMC are routinely employed in compressible tablet preparations for improving flow properties of the tablet and to achieve sustained release of an active ingredient.

In view of the following, Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U. S. ____ (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the

marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

It is submitted that a *prima facie* case of obviousness has not been established because whether taken alone, or in combination, neither of Anderson and Remington's in view of Alderman or Qui et al. and Remington's in view of Alderman teach or suggest every element of the presently pending claims as required by *In re Wilson*.

As discussed, Applicants submit that each of the presently pending claims presently include ***a granulate and a hydroxypropylmethyl cellulose external to the granulate***. According to the present subject matter, the granulate may comprise an active ingredient and a binder. Although, according to the present

subject matter, the binder may be a hydroxypropylmethyl cellulose, Applicants note that the present subject matter also includes additional hydroxypropylmethyl cellulose external to, i.e., separate from, the granulate. Applicants respectfully submit that as a result of the presently recited granulate and HPMC external to the granulate: the desired dissolution profile of a tablet according to the present subject matter may vary without remaking the granule composition; the granulate can be manufactured in bulk and than many batches of a tablet may be prepared, each having a different dissolution profile depending on the amount of HPMC added to the mixture; and no specific granulete size is required for the resulting tablets and consequently, the process of manufacture is significantly easier to implement than a process in which the HPMC is part of the granule composition.

Each of Anderson, Qui et al. and Remington's are discussed above. As discussed, whether taken alone or in combination, neither Anderson and Remington's nor Qui et al. and Remington's teach or suggest every element of the presently pending claims.

Alderman does not remedy the deficiencies of Anderson and Remington's or Qui et al. and Remingtons. Alderman is directed to solid tablets of a therapeutically active composition that exhibit sustained release properties when compressed with a fine particle sized hydroxypropyl cellulose. *See* Alderman at the abstract. Like Anderson, Qui et al. and Remington's, Alderman does not teach or suggest a granulate and a hydroxypropylmethyl cellulose external to the granulate. Therefore, whether taken alone or in combination, neither Anderson

and Remington's in view of Alderman nor Qui et al. and Remington's in view of Alderman teach or suggest every element of the presently pending claims.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, neither Anderson and Remington's in view of Alderman nor Qui et al. and Remington's in view of Alderman render claims the presently claimed subject matter obvious within the meaning of 35 USC § 103 (a). Accordingly, the Examiner is respectfully to withdraw this rejection.

CONCLUSION

In view of the foregoing, Applicant submits that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP

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Gary M. Nath
Registration No. 26,965
Susanne M. Hopkins
Registration No. 33,247
Ari G. Zytcer
Registration No. 57,474
Customer No. 20529

THE NATH LAW GROUP
112 S. West Street
Alexandria, VA 22314
Tel: (703) 548-6284
Fax: (703) 683-8396